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Short Communication

Body composition in patients with classical homocystinuria: body mass relates to homocysteine and choline metabolism

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ABSTRACT

Introduction: Classical homocystinuria is a rare genetic disease caused by cystathionine β-synthase deficiency, resulting in homocysteine accumulation. Growing evidence suggests that reduced fat mass in patients with classical homocystinuria may be associated with alterations in choline and homocysteine pathways. This study aimed to evaluate the body composition of patients with classical homocystinuria, identifying changes in body fat percentage and correlating findings with biochemical markers of homocysteine and choline pathways, lipoprotein levels and bone mineral density (BMD) T-scores.

Methods: Nine patients with classical homocystinuria were included in the study. Levels of homocysteine, methionine, cysteine, choline, betaine, dimethylglycine and ethanolamine were determined. Body composition was assessed by bioelectrical impedance analysis (BIA) in patients and in 18 controls. Data on the last BMD measurement and lipoprotein profile were obtained from medical records.

Results: Of 9 patients, 4 (44%) had a low body fat percentage, but no statistically significant differences were found between patients and controls. Homocysteine and methionine levels were negatively correlated with body mass index (BMI), while cysteine showed a positive correlation with BMI ($p < 0.05$). There was a trend between total choline levels and body fat percentage ($r = 0.439$, $p = 0.07$). HDL cholesterol correlated with choline and ethanolamine levels ($r = 0.757$, $p = 0.049$; $r = 0.847$, $p = 0.016$, respectively), and total cholesterol also correlated with choline levels ($r = 0.775$, $p = 0.041$). There was no association between BMD T-scores and body composition.

Conclusions: These results suggest that reduced fat mass is common in patients with classical homocystinuria, and that alterations in homocysteine and choline pathways affect body mass and lipid metabolism.

1. Introduction

Homocysteine is a toxic amino acid formed from methionine. High levels of homocysteine are associated with an increased incidence of several diseases, such as stroke, heart failure, coronary heart disease, dementia, and bone fractures (Homocysteine Studies Collaboration, 2002; Mudd et al., 1985). There are three main pathways by which homocysteine can be removed. In the transsulfuration pathway, homocysteine is irreversibly degraded by the action of the enzyme cystathionine beta-synthase (CβS; EC 4.2.1.22). It can also be remethylated by the ubiquitous methionine synthase (MS; EC 2.1.1.13), an enzyme dependent on vitamin B12 and folate, or by the liver/kidney specific betaine–homocysteine methyltransferase (BHMT; EC 2.1.1.5) using betaine. Betaine can be either derived from the diet or formed by oxidation of choline, a key nutrient in lipid metabolism.

Abbreviations: BIA, bioelectrical impedance analysis; BMD, bone mineral density; BMI, body mass index; CβS, cystathionine beta-synthase; DXA, dual-energy X-ray absorptiometry; ESPEN, European Society for Clinical Nutrition and Metabolism; HCPA, Hospital de Clínicas de Porto Alegre; HPLC, high performance liquid chromatography; IQ, interquartile range; SPSS, Statistical Package for the Social Sciences.

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Classical homocystinuria (OMIM 236200) is an autosomal recessive inborn error of metabolism caused by a deficiency in CβS, which results in increased plasma levels of homocysteine and methionine and decreased cysteine levels. It is a rare disease, with a worldwide prevalence estimated at 1:344,000 individuals (Mudd et al., 2001). Treatment includes pharmacological doses of pyridoxine (CβS cofactor), folic acid, vitamin B12, and, in some cases, betaine and also a methionine-restricted diet (Schiff and Blom, 2012). A large study on the natural history of the disease described equal proportions of patients responsive and unresponsive to pyridoxine (Mudd et al., 1985).

In addition to the classic manifestations (ectopia lentis, thromboembolism, mental retardation, and osteoporosis), patients with classical homocystinuria are tall and have a lean biotype (Brenton et al., 1972; Mudd et al., 1985). Until recently, it was believed that bone abnormalities were responsible for this phenotype. However, growing evidence suggests that these patients have reduced fat mass, associated with alterations in choline and homocysteine pathways.

In an animal model of classical homocystinuria, a marked decrease in adipose tissue was described as being associated with low levels of cysteine (Gupta and Kruger, 2011). Betaine and choline have also been associated with body composition, weight gain and lipid metabolism, both in healthy individuals and in experimental studies (Konstantinova et al., 2008; Teng et al., 2012; Wu et al., 2012). Moreover, there is evidence that choline and homocysteine metabolisms may overlap with respect to their relation to body weight (Zeisel, 2012). Given that the amount of body fat is closely related to bone mineral density (BMD), these changes could have important clinical implications in classical homocystinuria (Reid, 2008).

Despite the evidence from animal studies, this has not been studied in patients with classical homocystinuria. The objective of this study was to evaluate the body composition of patients with classical homocystinuria, identifying changes in body fat percentage and correlating findings with biochemical markers of homocysteine and choline pathways, lipoprotein levels and BMD T-scores.

2. Subjects and methods

The present study was approved by the Research Ethics Committee of Hospital de Clínicas de Porto Alegre (HCPA), Brazil, and the procedures were conducted after written informed consent was obtained from all subjects or their caretakers.

2.1. Study sample

Nine Brazilian patients with classical homocystinuria from 7 unrelated families were included in the study (median age = 26 years; IQ25–75 = 21–28 years). All patients had a late diagnosis (median age = 9 years; IQ25–75 = 6.25–12 years); 4 patients (44%) already had at least 3 systems compromised at diagnosis. Parental consanguinity was reported by 3/9 (33.3%) families.

At the time of study inclusion, all patients (aging 17–35 years) were receiving some type of treatment: pyridoxine (n = 7), folic acid (n = 8), betaine (n = 8), acetylsalicylic acid (n = 8), dietary methionine restriction (n = 9), and supplementation with a methionine-free formula (n = 2). However, most patients had not achieved adequate metabolic control (Table 1). Seven patients were unresponsive to pyridoxine, one was partially responsive (patient #4), and one was responsive (patient #3).

In addition, 18 healthy subjects (volunteers recruited from the institution) matched for gender and age, served as controls for bioelectrical impedance analysis (BIA) only. The controls had a median age of 25 years (IQ25–75 = 21–30 years).

The levels of homocysteine and methionine in the last 5 years (cysteine was unavailable) were obtained for 7 patients. For patient #7 these values were unavailable. Because patient #9 had a recent diagnosis, 3-year results of homocysteine and methionine measurements were obtained. Data on the last BMD measurement (T-score at the lumbar spine and femur), lipoprotein profile (triglycerides and HDL, LDL and total cholesterol) and clinical history were obtained from medical records. All patients had their diagnosis of classical homocystinuria based on the coexistence of hypermethioninemia and/or hyperhomocysteinemia and a positive cyanide-nitroprusside test, in addition to a clinical picture compatible with classical homocystinuria.

2.2. Assessment of body composition

Body composition was assessed in patients and controls in a single appointment by means of BIA (Biodynamics, 310e, Biodynamics Inc., Seattle, USA). Weight and height were measured and used to calculate BMI. BIA was performed using the tetrapolar method and following the recommendations of the European Society for Clinical Nutrition and Metabolism (ESPEN) (Kyle et al., 2004b). Based on the results obtained, body fat percentage was classified according to the cut-off points established by Heyward and Wagner (2004).

2.3. Assessment of BMD by dual-energy X-ray absorptiometry

BMD was assessed at the lumbar spine (L1–L4) and proximal and total femur by dual-energy X-ray absorptiometry (DXA) (GE—Lunar Prodigy, USA) at HCPA Department of Radiology. BMD was expressed as T-scores.

2.4. Laboratory assessment

Fasting blood was collected in EDTA tubes on the same day as BIA and anthropometry. Plasma was separated after centrifugation at 3000 rpm for 15 min. Total homocysteine, methionine and cysteine

Table 1
Results of the biochemical assessment in plasma and BMD of patients with classical homocystinuria (n = 9).

Patient	Current age (years)	Hcy	Met	Cys	Free betaine	Free choline	Total choline	Free ethanolamine	Total ethanolamine	Free DMG	T score − BMD	
		(μmol/L)			(uM)						Spine	Femur
1a	31	321.73	593.30	124.97	12.2	4.81	297	7.28	14.4	3.89	−2.6	−1.9
1b	35	186.64	88.50	354.63	229.5	9.34	208	9.55	8.7	112	0.9	−0.9
1c	26	322.23	630.50	138.82	19.2	5.53	209	8.14	12.5	2.38	−1.4	−1.3
2	22	109.76	624.60	226.49	174	10.8	295	7.9	11.8	37.75	−0.5	−0.8
3	18	10.82	110.30	354.63	31.9	8.97	216	8.76	17.0	2.87	−1.3	NA
4	17	42.71	26.08	390.81	497.5	6.31	195	7.33	11.1	146.5	−1.4	0.2
5	21	233.86	915.03	206.93	432	12.4	184	8.81	9.9	81.5	−4.5	−2.4
6	28	48.65	69.20	349.62	585	9.75	322	7.05	16.4	53	NA	NA
7	26	66.10	29.0	370.43	49.9	5.60	218	6.29	11.7	5.2	NA	NA

Hcy: homocysteine, Met: methionine. Cys: cysteine, NA: data not available, BMD: bone mineral density, DMG: dimethylglycine.
Reference values of: Hcy: 5–15 μmol/L; Met: 5–30 μmol/L; Cys: 174–378 μmol/L (Skovby, 2003). Hcy target values for the treatment of classical homocystinuria are <20 μmol/L for pyridoxine-responsive patients and <60 μmol/L for the remaining patients (Wilcken, 2006).

plasma concentrations were measured by high performance liquid chromatography (HPLC).

Free choline, ethanolamine, betaine and dimethylglycine were simultaneously assayed in plasma after deproteinization by an LC–MS/MS method adapted from Holm et al. (2003). The analytical system consisted of an Acquity UPLC system (Waters, Milford, USA) coupled with an API 4000 QTRAP mass spectrometer (AB Sciex, Framingham, USA) with an Atlantis HILIC analytical column (2.1 × 100 mm, 3 μm) (Waters, Milford, USA). Total choline and ethanolamine were measured by the same method used for free choline and ethanolamine but after acid hydrolysis (HCl 6N, 100 °C, 90 min) of the sample, releasing bound forms.

2.5. Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS), version 17.0 for Windows®. Variables were expressed as median and interquartile range [25th–75th percentile (IQ25–75)] due to their asymmetric distribution. Spearman's correlation coefficient was used to evaluate the association between body fat percentage, biochemical markers, and BMD T-scores in patients. Between-group differences in fat mass were evaluated using the qui-square (χ^2) test. A value of $p < 0.05$ was considered significant.

3. Results

At assessment, patients had a median homocysteine level of 147.5 μmol/L (IQ25–75 = 43–299), a median methionine level of 351.5 μmol/L (IQ25–75 = 73–628), and a median cysteine level of 287.5 μmol/L (IQ25–75 = 155–354). The results of biochemical assessment and BMD measurement are shown in Table 1.

The assessment of body composition in patients is shown in Table 2. As expected, no difference was found in gender and age between patients and controls, but patients had a lower median BMI than controls (20.5 and 23.1 kg/m^2, respectively; $p = 0.027$). Of 9 patients, 4 (44%) had low body fat percentage according to BIA. Among controls, only 2 (11%) had low fat percentage, while the remaining had normal (n = 11; 61%) or high (n = 5; 28%) fat percentage. However, no statistically significant difference in the classification of fat percentage was found between patients and controls ($p = 0.138$).

Regarding homocystinuria patients only, homocysteine levels at assessment and their median values in the last 5 years correlated negatively with current BMI (r = −0.833, $p = 0.004$ and r = −0.881, $p = 0.004$, respectively), while current cysteine levels showed a positive correlation with BMI (r = 0.912, $p = 0.001$) (Fig. 1). Methionine levels at assessment also showed a negative correlation with BMI (r = −0.883, $p = 0.002$) (Fig. 1). There was a trend for correlation between total choline levels and body fat percentage (r = 0.439, $p = 0.07$). The remaining metabolites (free betaine, free choline, free dimethylglycine, and free and total ethanolamine) did not correlate with body fat percentage or BMI.

LDL and total cholesterol levels were normal in all patients, but 3 had low HDL levels. Total choline levels were associated with HDL and total cholesterol levels (r = 0.757, $p = 0.049$; r = 0.775, $p = 0.041$). HDL cholesterol was also associated with total ethanolamine levels (r = 0.847, $p = 0.016$).

Regarding BMD, T-score at the femur showed a positive correlation with cysteine (r = 0.741) and a negative correlation with homocysteine at assessment (r = −0.741), although these correlations did not reach statistical significance ($p = 0.09$). No correlation was found between BMD T-scores and BMI, fat mass and lean mass.

4. Discussion

This is the first study to evaluate the relationship between the main homocysteine and choline metabolites and body composition in patients with classical homocystinuria. Accumulating evidence showing that levels of cysteine, homocysteine, choline and betaine influence fat mass has led us to investigate this association in classical homocystinuria (Elshorbagy et al., 2008; Teng et al., 2012; Wu et al., 2012; Zeisel, 2012).

We chose BIA to assess body composition because it is a noninvasive method, with easy availability and broad clinical application. BIA uses a low-intensity electric current that passes through the body. The method is based on the concept that tissues rich in water and electrolytes are more resistant to the flow of an electric current than adipose tissue. By determining the content of total body water, it is possible to calculate the content of lean mass and fat mass (Kyle et al., 2004a; Pietrobelli and Tatò, 2005). The standard error of the estimate of body composition by BIA ranges from 3 to 5%. The main factor related to verification errors is whole body hydration status (Houtkooper et al., 1996; Kyle et al., 2004b).

In our study, the assessment of body composition showed that a high proportion of our patients with classical homocystinuria had a low body fat percentage, but no significant difference was detected between patients and controls. There are no population-based studies evaluating Brazilians' body composition through BIA or other specific method; we only found studies evaluating BMI, which does not accurately reflect body composition. Interestingly, in our study, only two patients were underweight according to BMI, which indicates a more marked decrease in adipose tissue than in total mass. One patient was obese. This patient was taking a metabolic formula and had good metabolic control, which may have contributed to this phenotype.

In a recent study conducted in South Korea, body composition of 5 well-controlled patients with classical homocystinuria was described by means of DXA (Lim and Lee, 2013). Although the authors did not describe the values for fat mass, they reported that these values were within the normal range. The fact that no abnormalities were observed

Table 2
BMI and body composition evaluated by BIA in classical homocystinuria patients (n = 9).

Patient	Sex	Age	Weight	Height	BMI		BIA	
		(years)	(kg)	(m)	(kg/m^2)	Classification	% body fat	Classification
1a	F	31	45.6	1.62	17.4	Underweight	23.5	Low
1b	M	35	62.2	1.74	20.5	Normal range	22.2	Upper
1c	F	26	46.4	1.64	17.2	Underweight	26.7	Mid
2	F	22	61.0	1.73	20.4	Normal range	16.6	Low
3	M	18	67.6	1.78	21.3	Normal range	11.9	Mid
4	M	17	65.0	1.68	23.0	Normal range	9.1	Low
5	M	21	61.4	1.80	18.9	Normal range	14.8	Mid
6	F	28	68.7	1.68	24,3	Normal range	23.6	Low
7	M	26	97.4	1.77	31.1	Obese class I	24.9	Obesity

BMI: body mass index; BIA: electrical bioimpedance. BMI was classified according to the World Health Organization (1998) criteria and the body fat percentage according to the cutoffs established by Heyward and Wagner (2004).

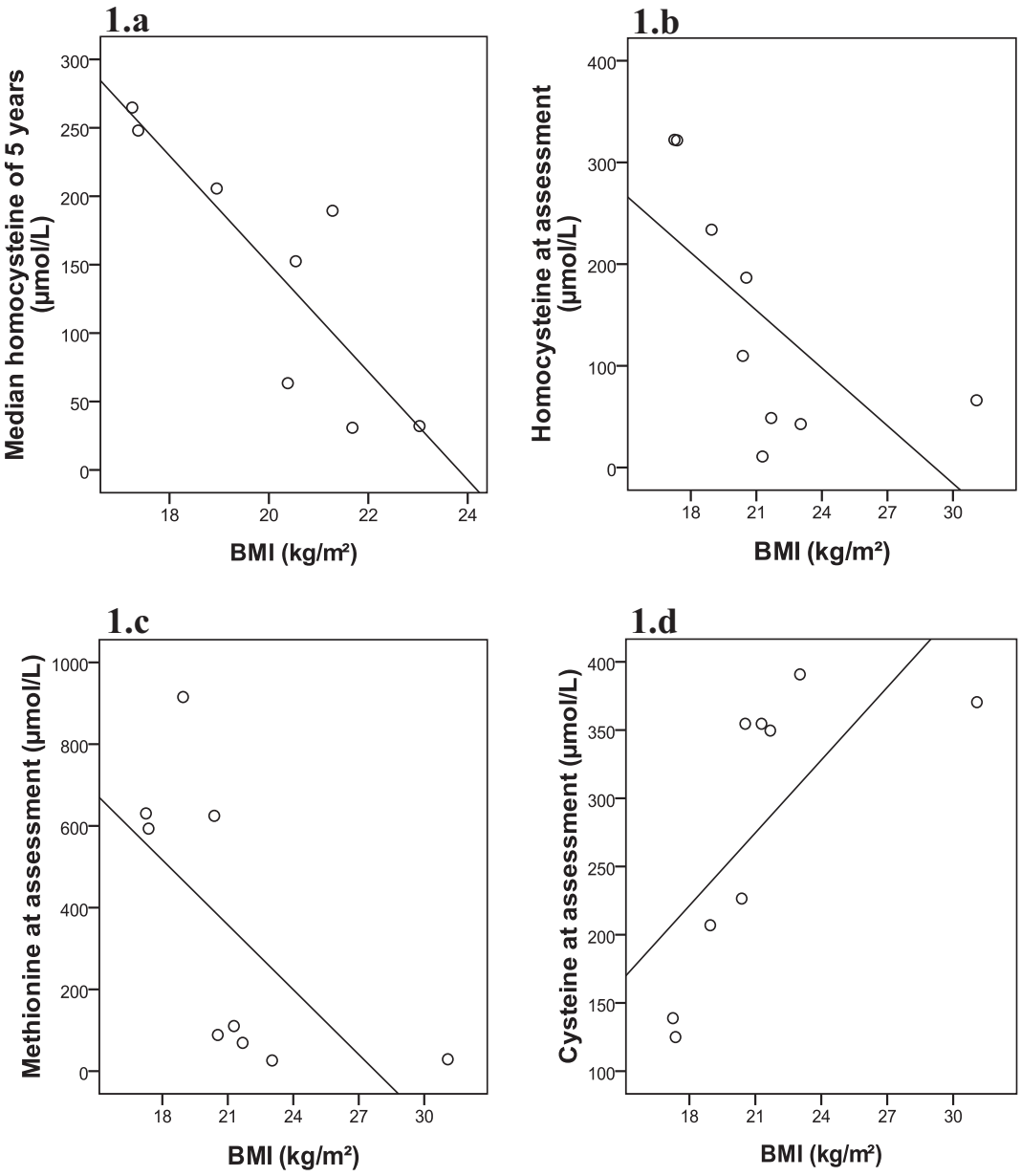

Fig. 1. Correlations between the main metabolites of homocysteine pathway and the body mass index (BMI). Solid lines represent the trend lines. 1.a) Median homocysteine values of the last 5 years correlate negatively with BMI ($r = -0.881$, $p = 0.004$). 1.b) Homocysteine levels at assessment also correlate negatively with BMI ($r = -0.833$, $p = 0.004$). 1.c) Methionine levels at assessment show a negative correlation with BMI ($r = -0.883$, $p = 0.002$). 1.d) Cysteine levels at assessment show a positive correlation with BMI ($r = 0.912$, $p = 0.001$).

in that group may be due to the following: a) as opposed to our patients, their patients had good metabolic control and a diet supplemented with cysteine, b) their sample size was even smaller than ours, and c) their study was not a controlled study.

In the present study, patients had lower BMI than controls. BMI is a measurement of total body mass. It is possible that both reductions in fat mass and in BMD observed in patients have contributed to this difference. We also found strong correlations between cysteine, methionine and homocysteine levels and BMI. A trend in the correlation between total choline levels and body fat percentage was also observed. The lack of a significant relationship between body fat and choline and its metabolites may have resulted from the small sample size, the influence of other body compartments, treatment with betaine, or limitations of the methods used. Another limitation of our study is that the biochemical variables were not evaluated in the control group. The analysis was also impaired by the lack of retrospective measures. Furthermore, it should be noted that the present sample was composed of treated patients, most of them receiving a diet supplemented with betaine. Even without good metabolic control, treatment can prevent complications and modify the natural history of the disease (Wilcken and Wilcken, 1997; Yap, 2003).

The association between cysteine and fat mass has been a recent target of studies investigating healthy individuals. In the large cohort of individuals in the Hordaland Homocysteine Study, serum concentration of cysteine showed a strong, positive and independent association with BMI and percentage of total body fat, even after adjustment for homocysteine concentration. Homocysteine, in turn, showed a negative correlation with BMI and body fat percentage. Methionine levels were not associated with body composition. The authors observed that the association between cysteine and fat mass was much stronger than that with homocysteine and concluded that this was the main determining factor for the percentage of total body fat in that population

(Elshorbagy et al., 2008). Another study performed in a large population showed that, after adjustment, methionine and homocysteine were not associated with BMI or serum lipids. Cysteine, however, was positively associated with BMI, total cholesterol and LDL-cholesterol (Elshorbagy et al., 2012).

The relation between choline levels and body fat percentage has been described in previous studies (Konstantinova et al., 2008; Teng et al., 2012). While choline is positively associated with fat mass, betaine is inversely associated. These nutrients are also related to energy expenditure and glucose, triglyceride and HDL levels (Konstantinova et al., 2008; Sparks et al., 2006; Teng et al., 2012). The positive association between HDL cholesterol and choline levels found in our study is consistent with previous observations, and may explain the low levels of HDL commonly observed in homocystinuria patients (Moat et al., 1999; Poloni et al., 2012).

In a recent study, the effect of CβS deficiency on body composition was evaluated in an animal model of classical homocystinuria. The authors observed that rats with CβS deficiency showed about 50% less fat mass than control animals, while the decrease in lean mass was small (9% in females and 14% in males). This decrease was associated with a significant decrease in cysteine levels and in the expression of hepatic *Scd-1* protein, which is a key lipogenic enzyme in the synthesis of monounsaturated fatty acids (Gupta and Kruger, 2011).

In our study, methionine levels showed a positive association with BMI. However, there is no evidence that methionine has a direct effect on body composition (Elshorbagy et al., 2011; Elshorbagy et al., 2012). A likely explanation for the correlation found in our study is that elevated methionine is merely a reflection of increased homocysteine levels, which both accumulate due to the defect. Methionine also influences the levels of cysteine, which appears to be an important mediator of body composition.

To evaluate the effect of fat mass reduction on bone health, we investigated the relationship between BMD T-scores and biochemical and body composition parameters, and found no statistical association of these parameters with bone density. However, cysteine appears to play a central role in the development of osteoporosis, since this disorder is not observed in other types of homocystinuria without cysteine deficiency (Wilcken, 2006). In the Hordaland cohort, cysteine levels were positively associated with BMD, but this association was lost when adjusted for lean mass and fat mass, demonstrating that the effect was likely mediated by body composition. Homocysteine concentration, in turn, was inversely related to bone mass in male individuals, independently of other variables (Elshorbagy et al., 2009). In our study, all patients with osteoporosis or osteopenia received a specific treatment, and this may have influenced the results obtained.

In conclusion, our results suggest that reduced fat mass is common in patients with classical homocystinuria, and that alterations in homocysteine and choline pathways may affect body mass and lipid metabolism. Furthermore, our study suggests that an effective treatment may be able to modify this phenotype. The decrease in body fat content may be one of the pathogenic mechanisms of osteoporosis in CβS deficiency; however, further studies are needed to prove this relation.

Conflict of interest

All authors confirm that they have no competing interests for declaration.

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